Journal Club:

Sacituzumab Govitecan in Hormone Receptor–Positive / Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer

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rapid communications

Sacituzumab Govitecan in Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer

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abstract

PURPOSE Hormone receptor–positive (HR+) human epidermal growth factor receptor 2–negative (HER2–) endocrine-resistant metastatic breast cancer is treated with sequential single-agent chemotherapy with poor outcomes. Sacituzumab govitecan (SG) is a first-in-class antibody-drug conjugate with an SN-38 payload targeting trophoblast cell-surface antigen 2, an epithelial antigen expressed in breast cancer.

METHODS In this global, randomized, phase III study, SG was compared with physician's choice chemotherapy (eribulin, vinorelbine, capecitabine, or gemcitabine) in endocrine-resistant, chemotherapy-treated HR+/HER2– locally recurrent inoperable or metastatic breast cancer. The primary end point was progression-free survival (PFS) by blinded independent central review.

RESULTS Patients were randomly assigned to receive SG (n = 272) or chemotherapy (n = 271). The median age was 56 years, 95% had visceral metastases, and 99% had a prior cyclin-dependent kinase 4/6 inhibitor, with three median lines of chemotherapy for advanced disease. Primary end point was met with a 34% reduction in risk of progression or death (hazard ratio, 0.66 [95% CI, 0.53 to 0.83; $P = .0003$]). The median PFS was 5.5 months (95% CI, 4.2 to 7.0) with SG and 4.0 months (95% CI, 3.1 to 4.4) with chemotherapy; the PFS at 6 and 12 months was 46% (95% CI, 39 to 53) *v* 30% (95% CI, 24 to 37) and 21% (95% CI, 15 to 28) *v* 7% (95% CI, 3 to 14), respectively. Median overall survival (first planned interim analysis) was not yet mature (hazard ratio, 0.84; $P = .14$). Key grade ≥ 3 treatment-related adverse events (SG *v* chemotherapy) were neutropenia (51% *v* 38%) and diarrhea (9% *v* 1%).

CONCLUSION SG demonstrated statistically significant PFS benefit over chemotherapy, with a manageable safety profile in patients with heavily pretreated, endocrine-resistant HR+/HER2– advanced breast cancer and limited treatment options.

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OUTLINE

01

Background

Overview of breast cancer

1st Cause of cancer death in women

0.052% Prevalence

56.4% HR(+)/HER2(-)

Proportion of breast cancer

69% HR(+)/HER2(−)

10% HR(+)/HER2(+)

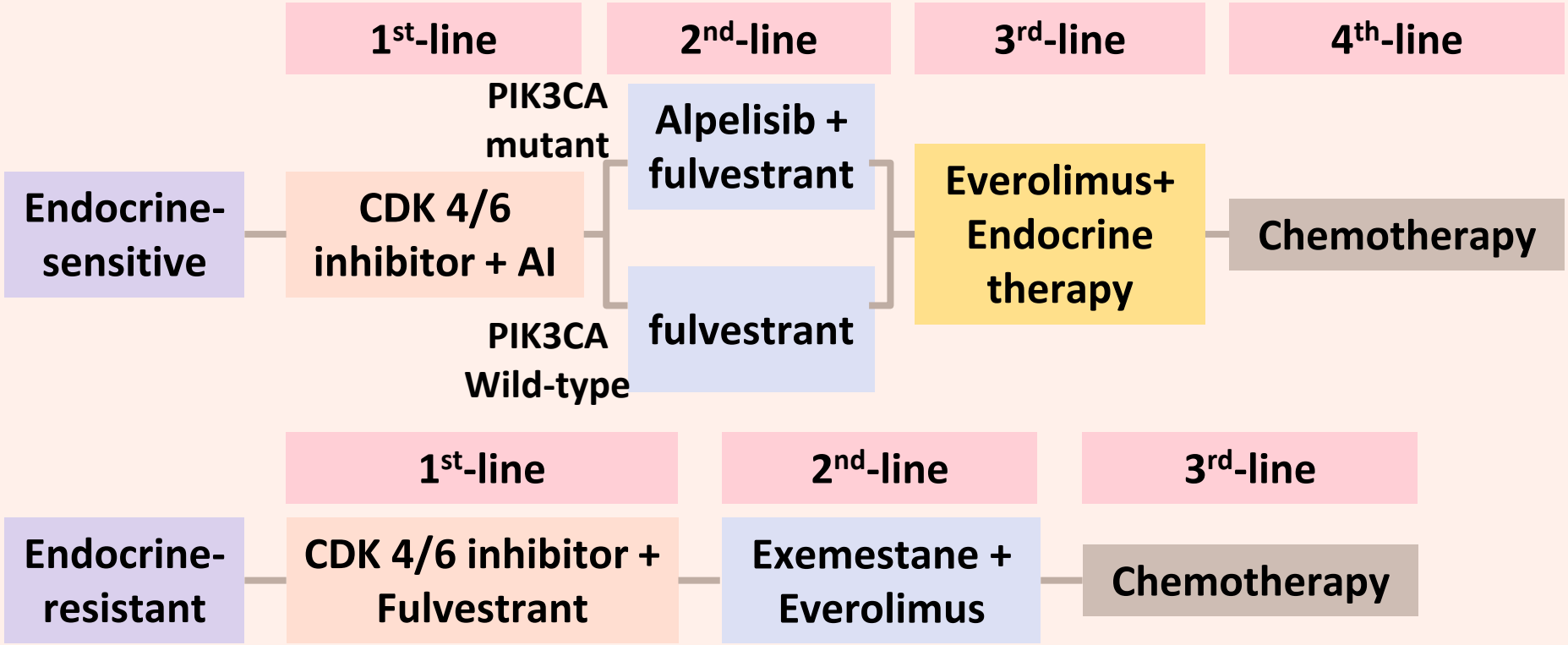
2013-2019
In the US

94.8% HR(+) HER2(−)

91.0% HR(+) HER2(+)

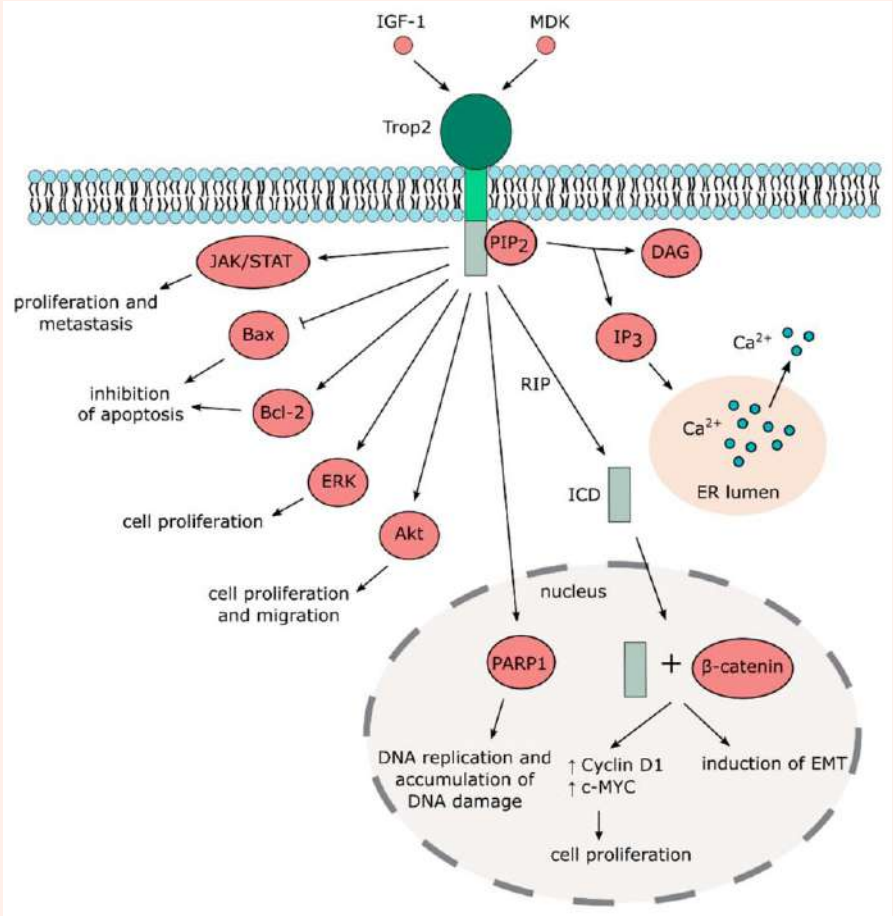
5-year survival

Preferred regimen of HR-positive / HER2-negative metastatic breast cancer



AI, Aromatase inhibitor

Trop2 and cancer



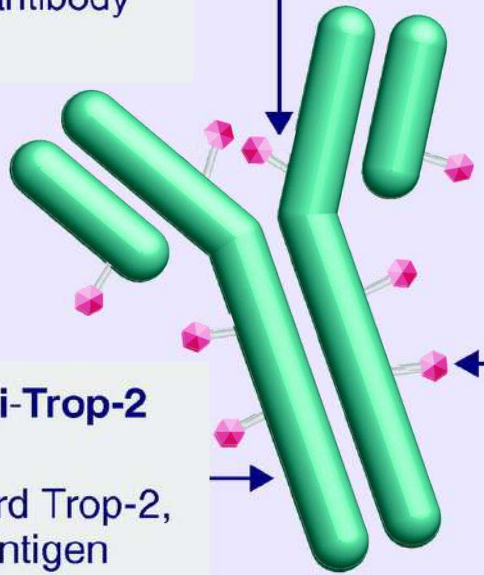
Sacituzumab Govitecan Mechanism

Linker for SN-38

- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7.6:1)

Trop-2 importance

- Trop-2 is seen in all BC type
- Most in HR+/HER2- and TNBC
- Link to tumor progression and poor prognosis



SN-38 payload

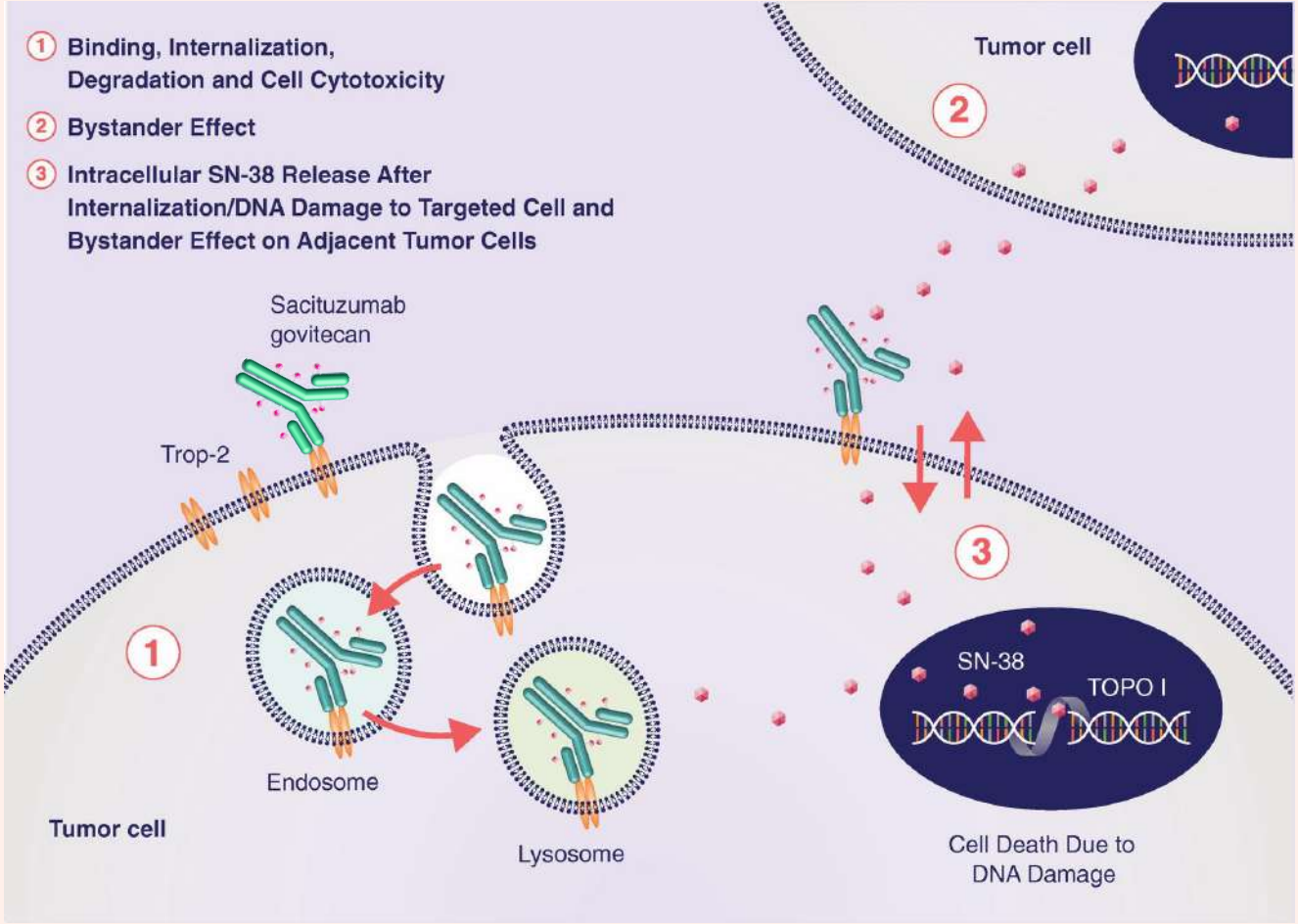
- Metabolite of Topo I inhibitor
- SN-38 more potent than parent compound, irinotecan

Humanized anti-Trop-2 antibody

- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

BC, breast cancer; TNBC, Triple negative breast cancer

Sacituzumab Govitecan Mechanism



Sacituzumab Govitecan phase I/II Basket trial

Population	Advanced epithelial cancer regardless of Trop-2 expression level
Intervention	Sacituzumab Govitecan 8,10,12,18 mg/kg
Prior therapy	One endocrine-based therapy and one chemotherapy
Outcome	ORR of 31.5% CBR of 44.4%

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ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial

A. Bardia[1], W. A. Messersmith[2], E. A. Kio[3], J. D. Berlin[4], L. Vahdat[5], G. A. Masters[6], R. Moroose[7], A. D. Santin[8], K. Kalinsky[9], V. Picozzi[10], J. O'Shaughnessy[11], J. E. Gray[12], T. Komiya[13], J. M. Lang[14], J. C. Chang[15], A. Starodub[16], D. M. Goldenberg[17], R. M. Sharkey[17], P. Maliakal[17], Q. Hong[17], W. A. Wegener[17], T. Goswami[17] & A. J. Ocean[5]*

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Available online 16 March 2021

Background: Sacituzumab govitecan (SG), a trophoblast cell surface antigen-2 (Trop-2)-directed antibody-drug conjugate, has demonstrated antitumor efficacy and acceptable tolerability in a phase I/II multicenter trial (NCT01631552) in patients with advanced epithelial cancers. This report summarizes the safety data from the overall safety population (OSP) and efficacy data, including additional disease cohorts not published previously.

Patients and methods: Patients with refractory metastatic epithelial cancers received intravenous SG (8, 10, 12, or 18 mg/kg) on days 1 and 8 of 21-day cycles until disease progression or unacceptable toxicity. Endpoints for the OSP included safety and pharmacokinetic parameters with investigator-evaluated objective response rate (ORR per RECIST 1.1), duration of response, clinical benefit rate, progression-free survival, and overall survival evaluated for cohorts ($n > 10$ patients) of small-cell lung, colorectal, esophageal, endometrial, pancreatic ductal adenocarcinoma, and castrate-resistant prostate cancer.

Sacituzumab Govitecan in TNBC

Current problem?	No biomarker, Not HER2-low, Triple-negative MBC 2nd-line left chemotherapy
What's new?	New 2nd-line Antibody-drug conjugate
Population	Triple-negative MBC, previous treated with taxanes
Outcome	PFS without brain metastasis, OS, ORR, safety

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

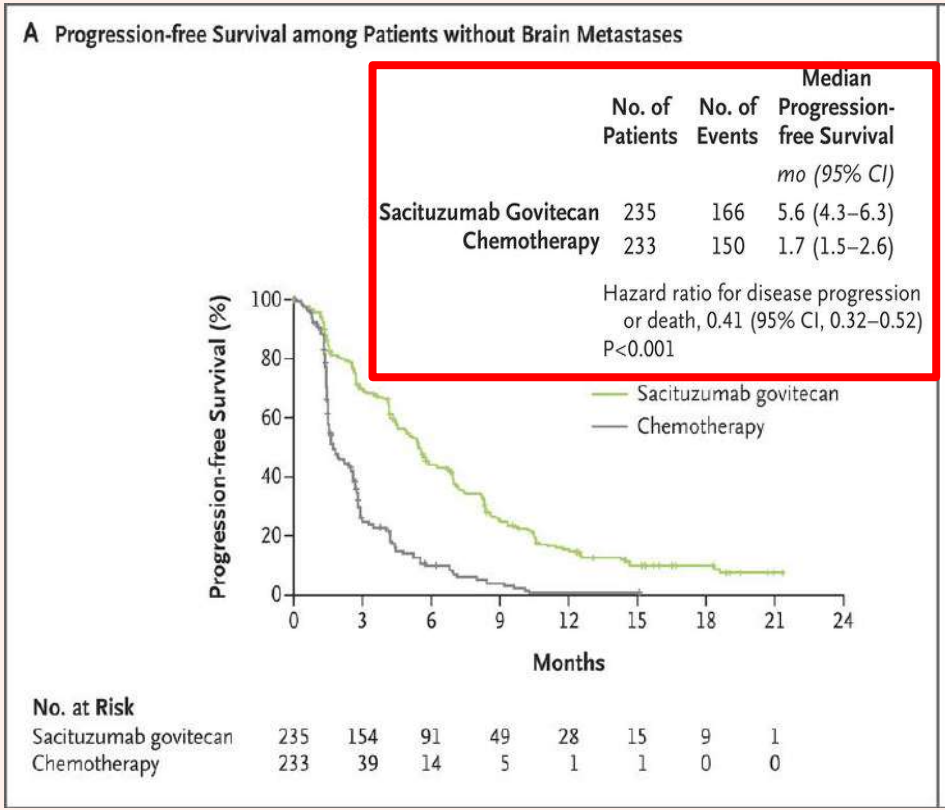
A. Bardia, S.A. Hurvitz, S.M. Tolaney, D. Loirat, K. Punie, M. Oliveira, A. Brufsky, S.D. Sardesai, K. Kalinsky, A.B. Zelnak, R. Weaver, T. Traina, F. Dalenc, P. Aftimos, F. Lynce, S. Diab, J. Cortés, J. O'Shaughnessy, V. Diéras, C. Ferrario, P. Schmid, L.A. Carey, L. Gianni, M.J. Piccart, S. Loibl, D.M. Goldenberg, Q. Hong, M.S. Olivo, L.M. Itri, and H.S. Rugo, for the ASCENT Clinical Trial Investigators*

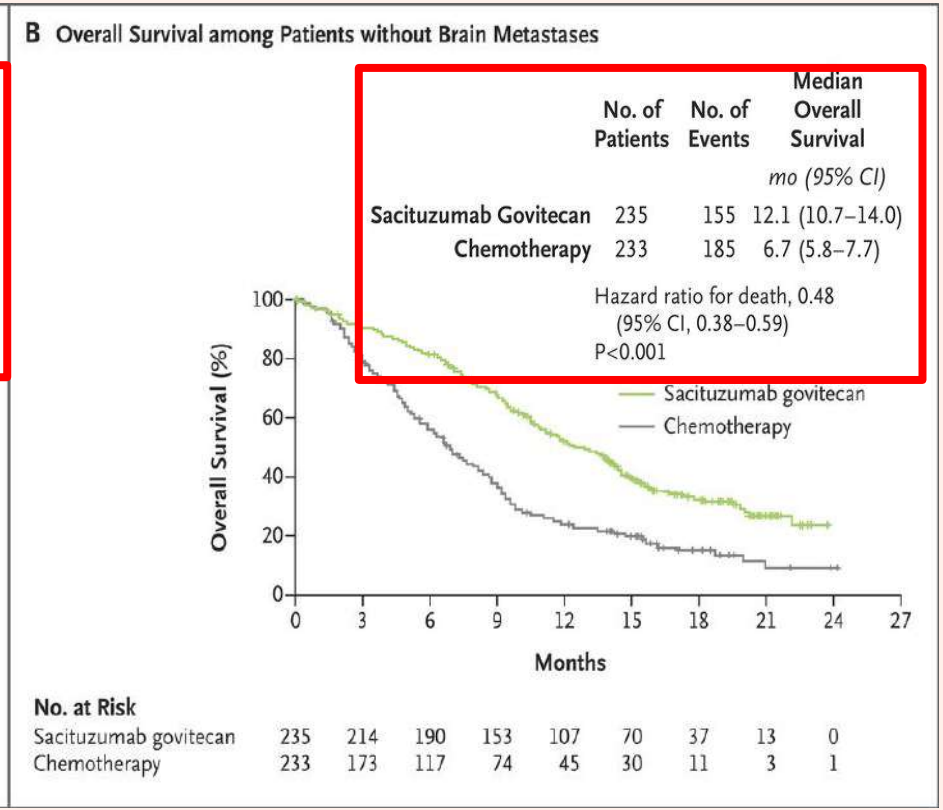
ABSTRACT

BACKGROUND

Patients with metastatic triple-negative breast cancer have a poor prognosis. Sacituzumab govitecan is an antibody–drug conjugate composed of an antibody targeting the human trophoblast cell-surface antigen 2 (Trop-2), which is expressed in the majority of breast cancers, coupled to SN-38 (topoisomerase I inhibitor) through a proprietary hydrolyzable linker.

PFS and OS in patients without brain metastases

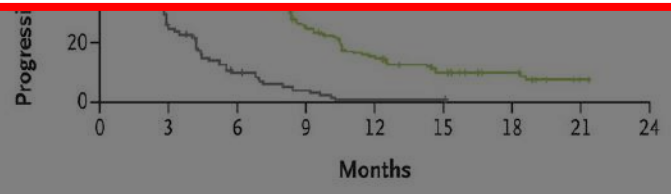




PFS and OS in patients without brain metastases

	No. of Patients	No. of Events	Median Progression-free Survival
			mo (95% CI)
Sacituzumab Govitecan	235	166	5.6 (4.3–6.3)
Chemotherapy	233	150	1.7 (1.5–2.6)

Hazard ratio for disease progression or death, 0.41 (95% CI, 0.32–0.52)
P<0.001

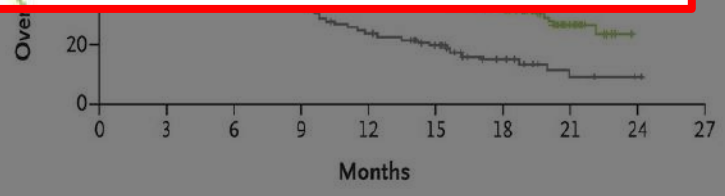


No. at Risk

Sacituzumab govitecan	235	154	91	49	28	15	9	1
Chemotherapy	233	39	14	5	1	1	0	0

	No. of Patients	No. of Events	Median Overall Survival
			mo (95% CI)
Sacituzumab Govitecan	235	155	12.1 (10.7–14.0)
Chemotherapy	233	185	6.7 (5.8–7.7)

Hazard ratio for death, 0.48 (95% CI, 0.38–0.59)
P<0.001



No. at Risk

Sacituzumab govitecan	235	214	190	153	107	70	37	13	0
Chemotherapy	233	173	117	74	45	30	11	3	1

Summary treatment efficacy

Table 2. Summary of Treatment Efficacy, as Determined by Independent Central Review.*

Variable	Patients without Brain Metastases		Full Population†	
	Sacituzumab Govitecan (N=235)	Chemotherapy (N=233)	Sacituzumab Govitecan (N=267)	Chemotherapy (N=262)
Median progression-free survival (95% CI) — mo	5.6 (4.3–6.3)	1.7 (1.5–2.6)	4.8 (4.1–5.8)	1.7 (1.5–2.5)
Hazard ratio for disease progression or death (95% CI)	0.41 (0.32–0.52)‡		0.43 (0.35–0.54)	
Median overall survival (95% CI) — mo	12.1 (10.7–14.0)	6.7 (5.8–7.7)	11.8 (10.5–13.8)	6.9 (5.9–7.7)
Hazard ratio for death (95% CI)	0.48 (0.38–0.59)‡		0.51 (0.41–0.62)	
Objective response — no. of patients (%)§	82 (35)	11 (5)	83 (31)	11 (4)
Complete response	10 (4)	2 (1)	10 (4)	2 (1)
Partial response	72 (31)	9 (4)	73 (27)	9 (3)
Clinical benefit — no. of patients (%)¶	105 (45)	20 (9)	108 (40)	21 (8)
Stable disease — no. of patients (%)	81 (34)	62 (27)	96 (36)	71 (27)
Stable disease for ≥6 mo	23 (10)	9 (4)	25 (9)	10 (4)
Progressive disease — no. of patients (%)	54 (23)	89 (38)	65 (24)	100 (38)
Response could not be evaluated — no. of patients (%)‖	18 (8)	71 (30)	23 (9)	80 (31)
Median time to response (95% CI) — mo	1.5 (0.7–10.6)	1.5 (1.3–4.2)	1.5 (0.7–10.6)	1.5 (1.3–4.2)
Median duration of response (95% CI) — mo	6.3 (5.5–9.0)	3.6 (2.8–NE)	6.3 (5.5–9.0)	3.6 (2.8–NE)
Hazard ratio (95% CI)	0.39 (0.14–1.07)			

Summary treatment efficacy

Table 2. Summary of Treatment Efficacy, as Determined by Independent Central Review.*

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Hazard ratio for disease progression or death (95% CI)	0.41 (0.32–0.52)‡		0.43 (0.35–0.54)	
Median overall survival (95% CI) — mo	12.1 (10.7–14.0)	6.7 (5.8–7.7)	11.8 (10.5–13.8)	6.9 (5.9–7.7)
Hazard ratio for death (95% CI)	0.48 (0.38–0.59)‡		0.51 (0.41–0.62)	
Progressive disease — no. of patients (%)	54 (23)	89 (38)	65 (24)	100 (38)
Response could not be evaluated — no. of patients (%)‖	18 (8)	71 (30)	23 (9)	80 (31)
Median time to response (95% CI) — mo	1.5 (0.7–10.6)	1.5 (1.3–4.2)	1.5 (0.7–10.6)	1.5 (1.3–4.2)
Median duration of response (95% CI) — mo	6.3 (5.5–9.0)	3.6 (2.8–NE)	6.3 (5.5–9.0)	3.6 (2.8–NE)
Hazard ratio (95% CI)	0.39 (0.14–1.07)			

02

Methods

Study design

Phase III, open-label, randomized study

≥ 18 y/o with HR+/HER2- mBC

- **2-4 prior systemic chemotherapy for mBC**
- **≥ 1 type of endocrine therapy + taxane + CDK 4/6 inhibitor**
- Measurable disease by RECIST 1.1

R
1 : 1

Sacituzumab govitecan
10mg/kg IV days 1 and 8
Every 21 days

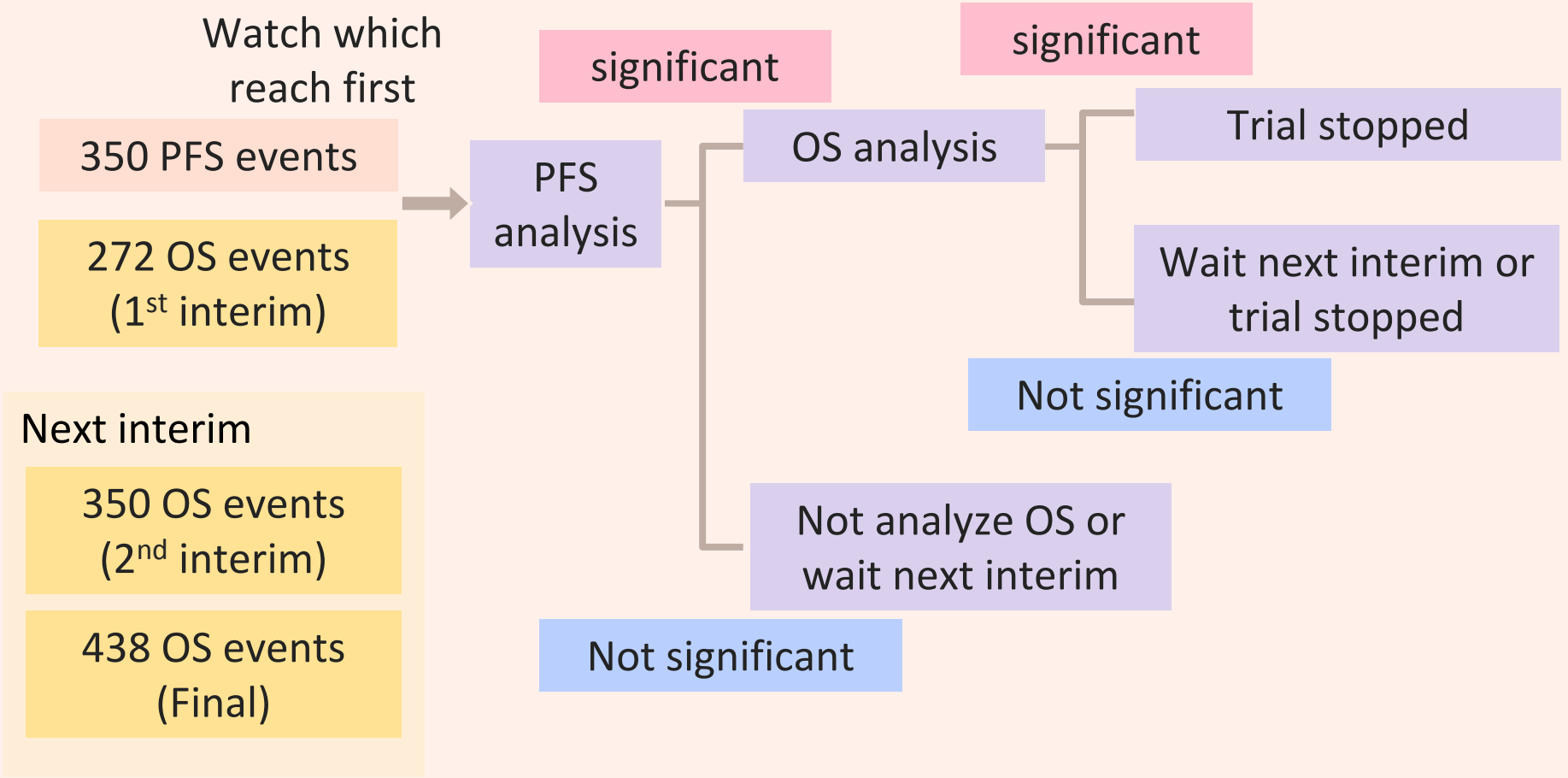
Physician's choice
(capecitabine, vinorelbine, gemcitabine or eribulin)

Primary endpoint:
PFS (BICR)
Secondary endpoint:
OS, ORR, CBR, DoR; safety

Stratification factors :
Prior chemotherapy regimens for metastatic disease (2 vs 3/4)
Visceral metastases (Y/N)
Prior endocrine treatment in the metastatic setting ≥ 6 months (Y/N)

PFS, Progression-free survival; BICR, Blinded independent central review; OS, overall survival; ORR, objective response rate; CBR, clinical benefit rate; DoR, Duration of response.

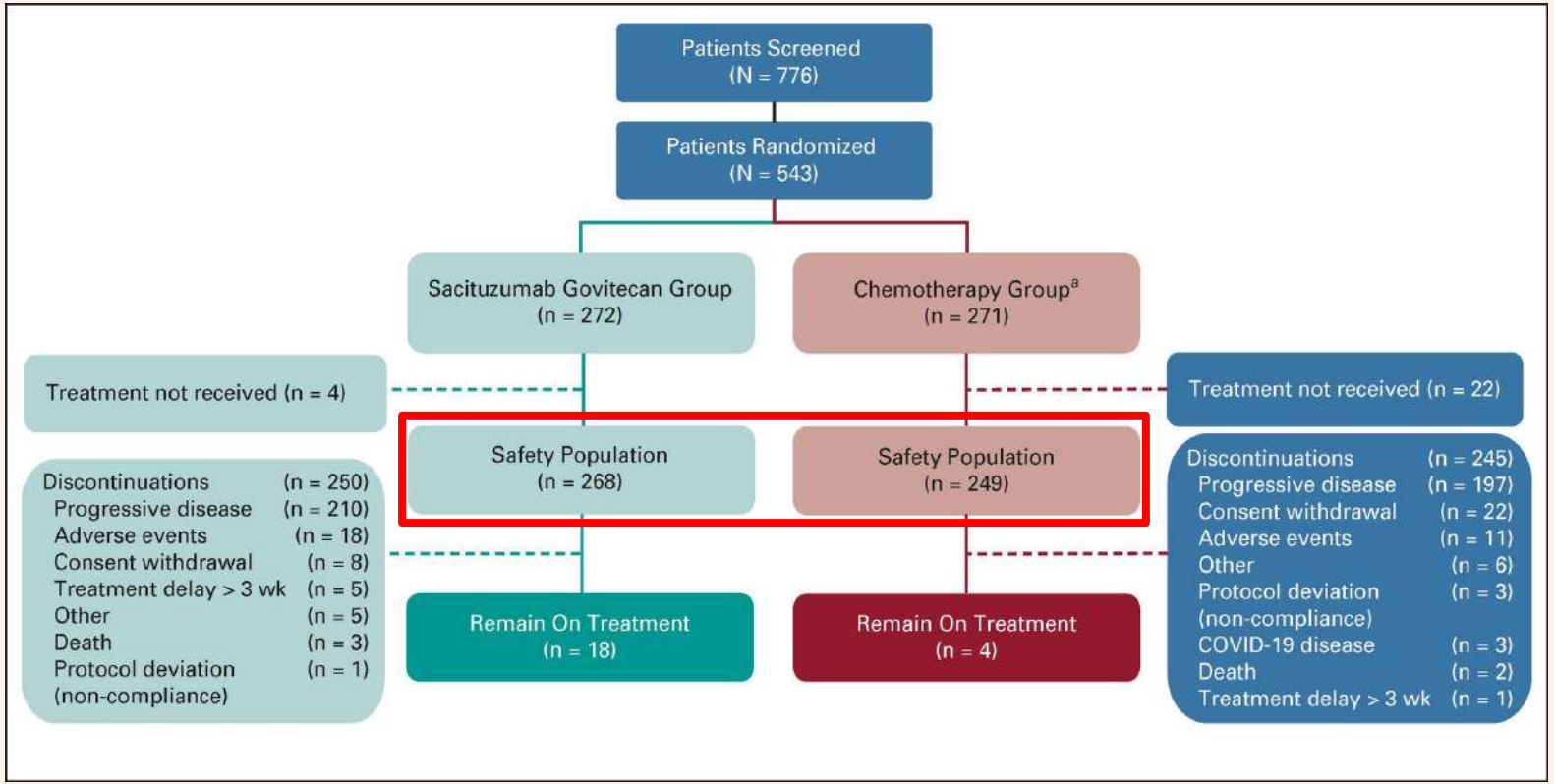
Statistical analysis



03

Results

CONSORT diagram



Chemotherapy group:

eribulin (n = 130), vinorelbine (n = 63), gemcitabine (n = 56), or capecitabine (n = 22)

Baseline Characteristics

TABLE 1. Baseline Characteristics and Treatment History of Patients

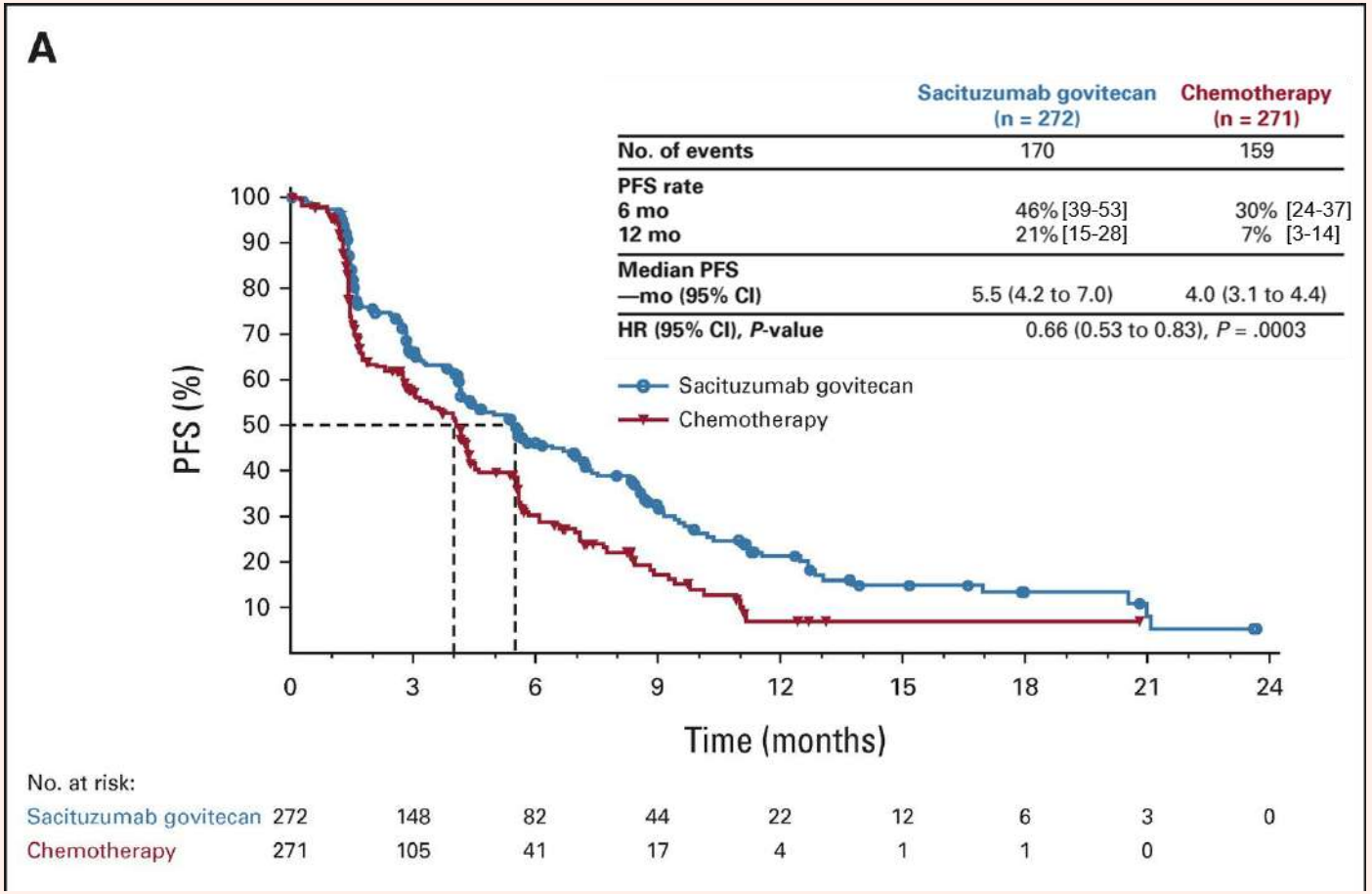
Characteristic	SG (n = 272)	Chemotherapy (n = 271)	All (N = 543)
Female, No. (%)	270 (99)	268 (99)	538 (99)
Median age, years (range)	57 (29-86)	55 (27-78)	56 (27-86)
Race or ethnic group, No. (%)			
White	184 (68)	178 (66)	362 (67)
Black	8 (3)	13 (5)	21 (4)
Asian	11 (4)	5 (2)	16 (3)
Others[a]	0	5 (2)	5 (1)
Not specified[b]	69 (25)	70 (26)	139 (26)
Visceral metastases at baseline, No. (%)	259 (95)	258 (95)	517 (95)
Liver metastases,[c] No. (%)	229 (84)	237 (87)	466 (86)
De novo MBC, No. (%)	78 (29)	60 (22)	138 (25)
Prior endocrine therapy in the metastatic setting > 6 months, No. (%)			
Yes	235 (86)	234 (86)	469 (86)
No	37 (14)	37 (14)	74 (14)
Prior CDK4/6i use, months, No. (%)			
≤ 12	161 (59)	166 (61)	327 (60)
> 12	106 (39)	102 (38)	208 (38)
Unknown	5 (2)	3 (1)	8 (1)
Median prior chemotherapy regimens in the metastatic setting, No. (%)[d]	3 (0-8)[d]	3 (1-5)[d]	3 (0-8)[d]
0	1 (< 1)	0	1 (< 1)
1	8 (3)	2 (1)	10 (2)
2	104 (38)	118 (43)	222 (41)
≥ 3	159 (58)	151 (56)	310 (57)

Baseline Characteristics

TABLE 1. Baseline Characteristics and Treatment History of Patients

Characteristic	SG (n = 272)	Chemotherapy (n = 271)	All (N = 543)
Median prior chemotherapy regimens, No. (range)	4 (1-9)	4 (2-7)	4 (1-9)
Median prior anticancer regimens,[e] No. (range)	7 (3-17)	7 (3-16)	7 (3-17)
Most common prior anticancer therapy,[e] No. (%)			
Palbociclib	238 (88)	228 (84)	466 (86)
Capecitabine	226 (83)	234 (86)	460 (85)
Fulvestrant	235 (86)	223 (82)	458 (84)
Cyclophosphamide	204 (75)	209 (77)	413 (76)
Paclitaxel	210 (77)	196 (72)	406 (75)
Letrozole	185 (68)	210 (77)	395 (73)
Tamoxifen	160 (59)	165 (61)	325 (60)
Doxorubicin[e]	149 (55)	134 (49)	283 (52)
Exemestane	142 (52)	134 (49)	276 (51)
Most common prior anticancer therapy class in the metastatic setting,[e] No. (%)			
Endocrine therapy	268 (99)	269 (99)	537 (99)
CDK4/6i	267 (98)	270 (> 99)	537 (99)
Targeted agent	181 (67)	172 (63)	353 (65)
Immunotherapy	21 (8)	15 (6)	36 (7)
Chemotherapy	271 (> 99)	271(100)	542 (> 99)
Most common prior chemotherapy agent in the metastatic setting,[e] No. (%)			
Capecitabine	221 (81)	232 (86)	453 (83)
Paclitaxel	174 (64)	147 (54)	321 (59)
Eribulin[e]	95 (35)	88 (33)	183 (34)

Primary end points - PFS



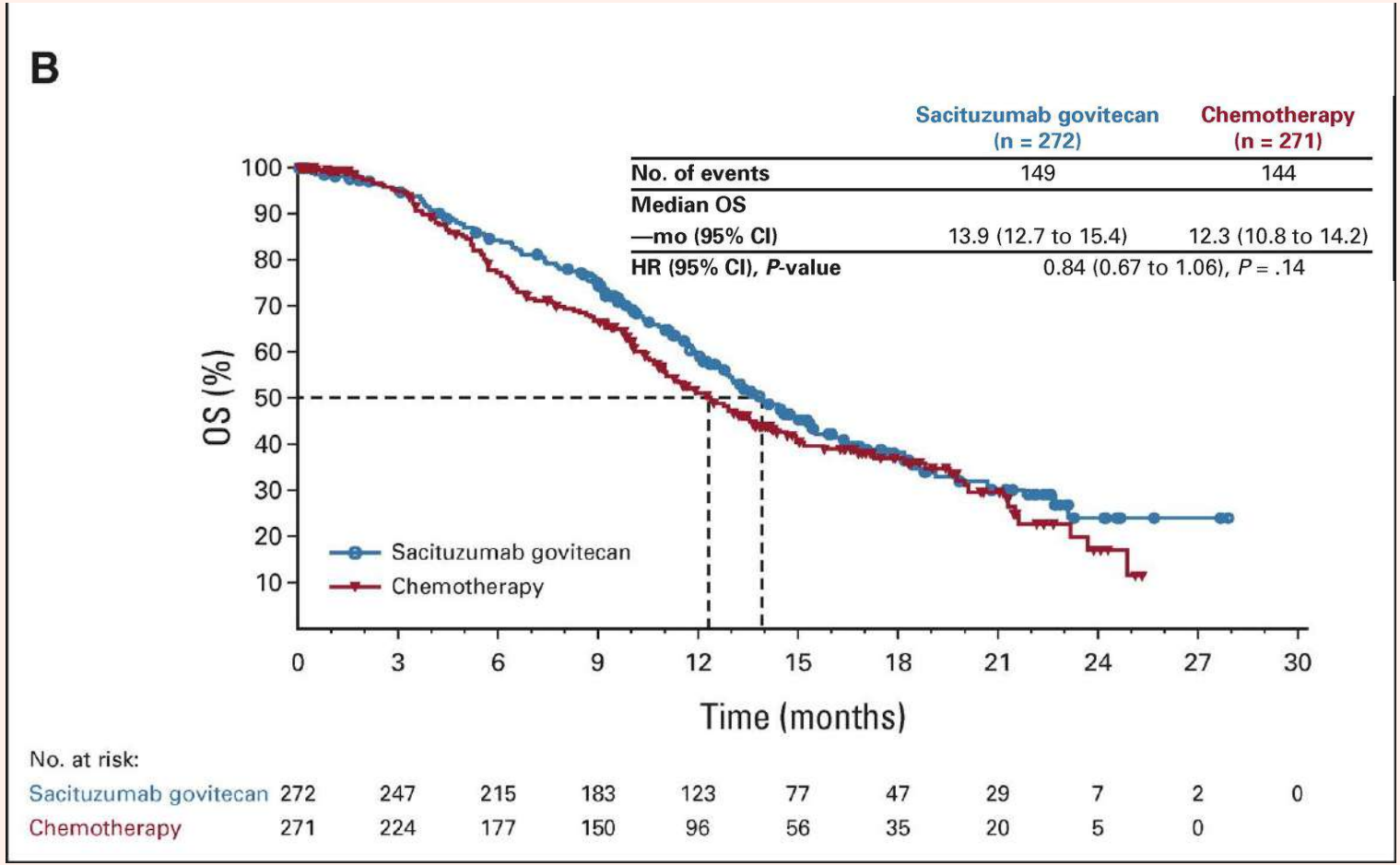
Primary end points - PFS

Treatment with SG showed a benefit over physician's choice in PFS, as assessed by BICR.

	Sacituzumab govitecan (n = 272)	Chemotherapy (n = 271)
No. of events	170	159
PFS rate		
6 mo	46% [39-53]	30% [24-37]
12 mo	21% [15-28]	7% [3-14]
Median PFS —mo (95% CI)	5.5 (4.2 to 7.0)	4.0 (3.1 to 4.4)
HR (95% CI), *P*-value	0.66 (0.53 to 0.83), *P* = .0003	

Treatment with SG showed a benefit over physician's choice at all landmark time.

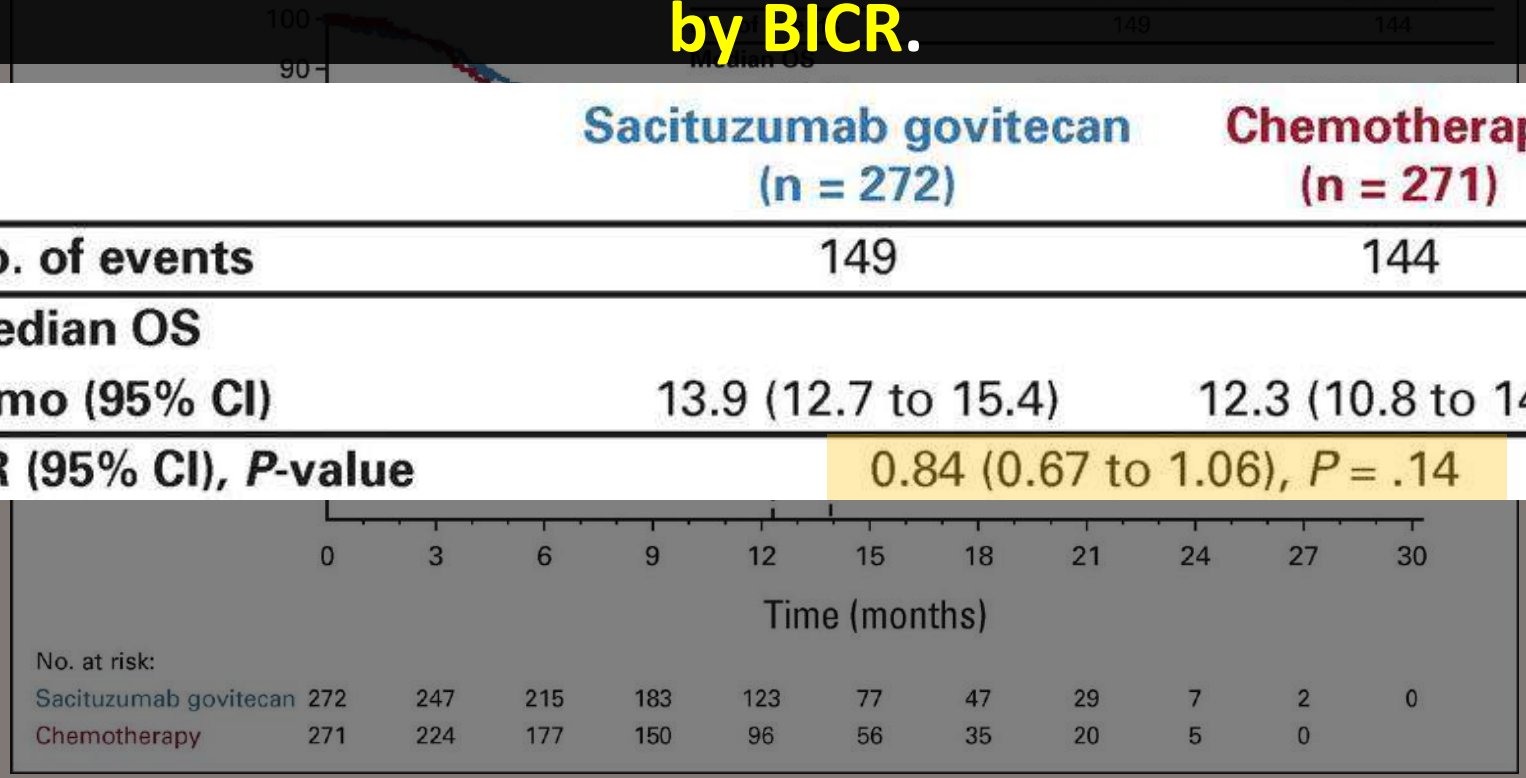
Secondary end points - OS



Secondary end points - OS

Treatment with SG didn't show a significant benefit over physician's choice in 1st-interim analysis of OS, as assessed by BICR.

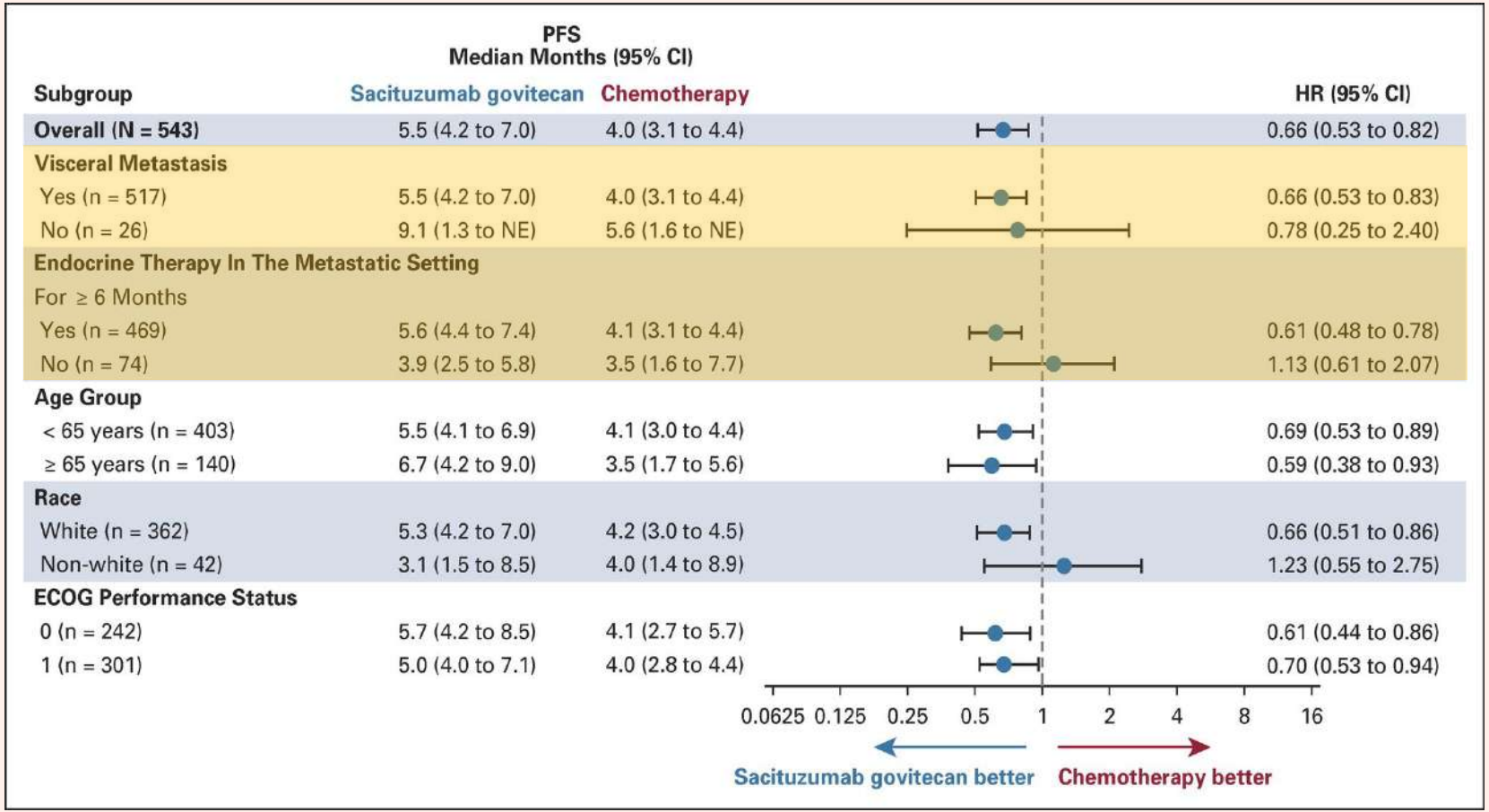
	Sacituzumab govitecan (n = 272)	Chemotherapy (n = 271)
No. of events	149	144
Median OS —mo (95% CI)	13.9 (12.7 to 15.4)	12.3 (10.8 to 14.2)
HR (95% CI), *P*-value	0.84 (0.67 to 1.06), *P* = .14	



Summary of treatment efficacy

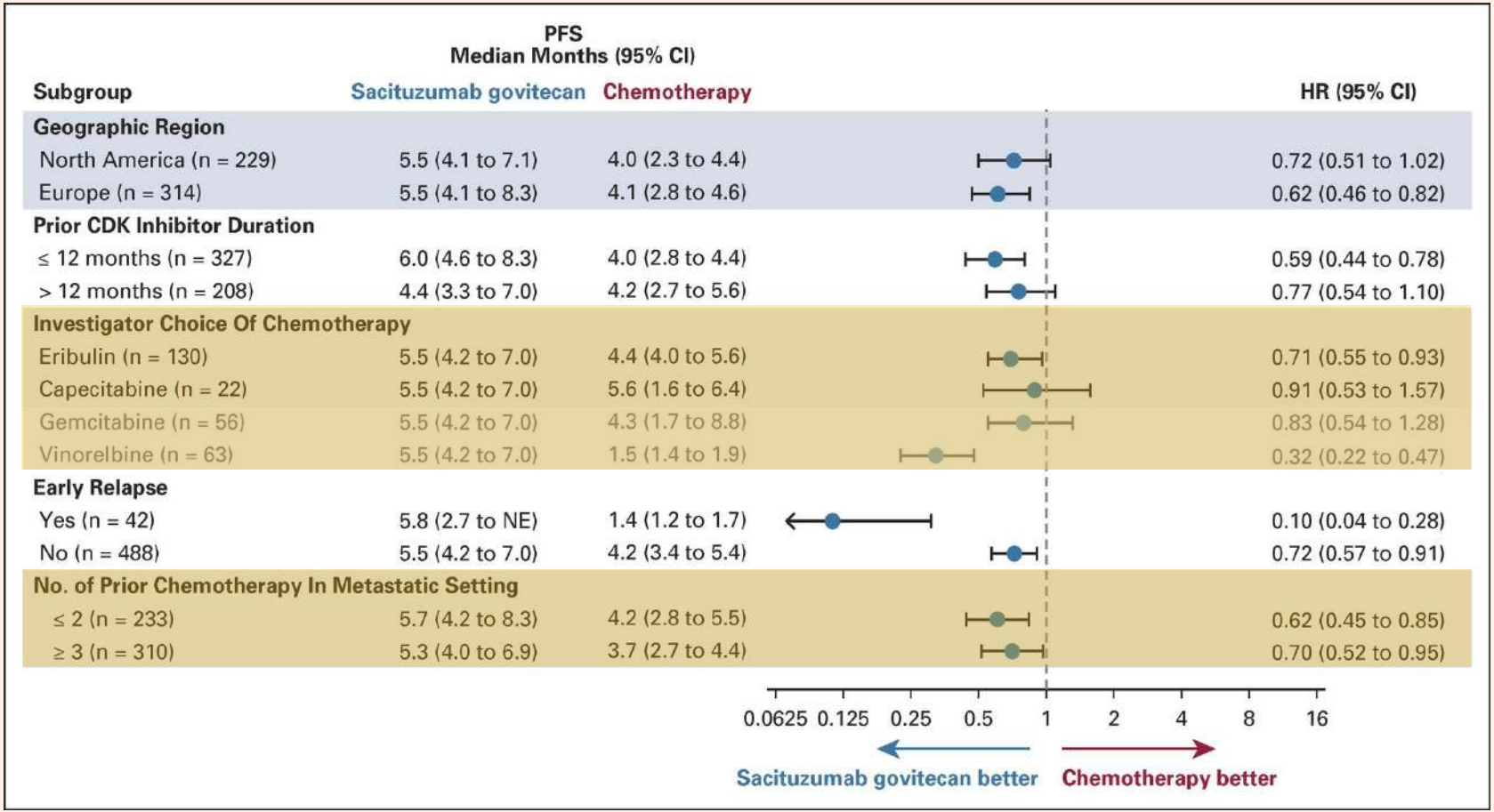
Efficacy Outcome	SG (n = 272)	Chemotherapy (n = 271)
Objective response rate, No. (%)	57 (21)	38 (14)
Best overall response, No. (%)		
Complete response	2 (1)	0
Partial response	55 (20)	38 (14)
Stable disease	142 (52)	106 (39)
Stable disease ≥ 6 months	35 (13)	21 (8)
Progressive disease	58 (21)	76 (28)
Not evaluable	15 (6)	51 (19)
CBR,[a] No. (%)	92 (34)	59 (22)
Median DOR, months (95% CI)	7.4 (6.5 to 8.6)	5.6 (3.8 to 7.9)

Subgroup analysis of PFS



Subgroup	PFS Median Months (95% CI) Sacituzumab govitecan	Chemotherapy	HR (95% CI)
Overall (N = 543)	5.5 (4.2 to 7.0)	4.0 (3.1 to 4.4)	0.66 (0.53 to 0.82)
Visceral Metastasis			
Yes (n = 517)	5.5 (4.2 to 7.0)	4.0 (3.1 to 4.4)	0.66 (0.53 to 0.83)
No (n = 26)	9.1 (1.3 to NE)	5.6 (1.6 to NE)	0.78 (0.25 to 2.40)
Endocrine Therapy In The Metastatic Setting For ≥ 6 Months			
Yes (n = 469)	5.6 (4.4 to 7.4)	4.1 (3.1 to 4.4)	0.61 (0.48 to 0.78)
No (n = 74)	3.9 (2.5 to 5.8)	3.5 (1.6 to 7.7)	1.13 (0.61 to 2.07)
Age Group			
< 65 years (n = 403)	5.5 (4.1 to 6.9)	4.1 (3.0 to 4.4)	0.69 (0.53 to 0.89)
≥ 65 years (n = 140)	6.7 (4.2 to 9.0)	3.5 (1.7 to 5.6)	0.59 (0.38 to 0.93)
Race			
White (n = 362)	5.3 (4.2 to 7.0)	4.2 (3.0 to 4.5)	0.66 (0.51 to 0.86)
Non-white (n = 42)	3.1 (1.5 to 8.5)	4.0 (1.4 to 8.9)	1.23 (0.55 to 2.75)
ECOG Performance Status			
0 (n = 242)	5.7 (4.2 to 8.5)	4.1 (2.7 to 5.7)	0.61 (0.44 to 0.86)
1 (n = 301)	5.0 (4.0 to 7.1)	4.0 (2.8 to 4.4)	0.70 (0.53 to 0.94)

Subgroup analysis of PFS



Safety-

AEs of Any Grade (≥ 10%) and Worst Grade 2 or Grade ≥ 3 (≥ 5%)

	SG (n = 268)			Chemotherapy (n = 249)		
Treatment-Related AE[a]	All Grade	Grade 2	Grade ≥ 3	All Grade	Grade 2	Grade ≥ 3
Hematologic, No. (%)						
Neutropenia[b]	188 (70)	45 (17)	136 (51)	134 (54)	29 (12)	94 (38)
Anemia[c]	91 (34)	44 (16)	17 (6)	62 (25)	31 (12)	8 (3)
Leukopenia[d]	37 (14)	7 (3)	23 (9)	23 (9)	8 (3)	13 (5)
Lymphopenia[e]	31 (12)	11 (4)	10 (4)	25 (10)	7 (3)	8 (3)
Febrile neutropenia	14 (5)	0	14 (5)	11 (4)	0	11 (4)
GI, No. (%)						
Diarrhea	152 (57)	56 (21)	25 (9)	41 (16)	12 (5)	3 (1)
Nausea	148 (55)	56 (21)	3 (1)	77 (31)	23 (9)	7 (3)
Vomiting	50 (19)	12 (4)	1 (< 1)	30 (12)	8 (3)	4 (2)
Constipation	49 (18)	8 (3)	0	36 (14)	8 (3)	0
Abdominal pain	34 (13)	12 (4)	2 (1)	17 (7)	4 (2)	0
Others, No. (%)						
Alopecia	123 (46)	105 (39)	0	41 (16)	18 (7)	0
Fatigue	100 (37)	37 (14)	15 (6)	73 (29)	31 (12)	6 (2)
Asthenia	53 (20)	26 (10)	5 (2)	37 (15)	19 (8)	2 (1)
Decreased appetite	41 (15)	9 (3)	1 (< 1)	34 (14)	13 (5)	1 (< 1)
Neuropathy[f]	23 (9)	8 (3)	3 (1)	38 (15)	16 (6)	6 (2)

Safety-EAIR of AE per PYE

Adverse Event	Sacituzumab Govitecan (N = 268) Per PYE	Chemotherapy (N = 249) Per PYE
Hematologic		
Neutropenia*		
PYE	42.5	36.8
EAIR (95% CI)	4.44 (3.83 to 5.13)	3.69 (3.10 to 4.37)
EAIR Difference vs. TPC (95% CI)	0.75 (-0.16 to 1.66)	
Anemia†		
PYE	85.7	60.0
EAIR (95% CI)	1.13 (0.92 to 1.38)	1.13 (0.88 to 1.44)
EAIR Difference vs. TPC (95% CI)	0 (-0.37 to 0.35)	
Leukopenia‡		
PYE	111.7	66.2
EAIR (95% CI)	0.34 (0.24 to 0.47)	0.38 (0.24 to 0.56)
EAIR Difference vs. TPC (95% CI)	-0.04 (-0.24 to 0.15)	
Diarrhea		
PYE	50.8	57.0
EAIR (95% CI)	3.27 (2.79 to 3.81)	0.98 (0.74 to 1.28)
EAIR Difference vs. TPC (95% CI)	2.29 (1.72 to 2.87)	
Nausea		
PYE	62.4	52.1
EAIR (95% CI)	2.52 (2.14 to 2.94)	1.67 (1.34 to 2.06)
EAIR Difference vs. TPC (95% CI)	0.85 (0.30 to 1.39)	
Alopecia		
PYE	62.3	56.1
EAIR (95% CI)	2.06 (1.71 to 2.44)	0.82 (0.60 to 1.09)
EAIR Difference vs. TPC (95% CI)	1.23 (0.80 to 1.68)	
Fatigue		
PYE	81.8	50.3
EAIR (95% CI)	1.27 (1.04 to 1.54)	1.63 (1.30 to 2.03)
EAIR Difference vs. TPC (95% CI)	-0.36 (-0.82 to 0.07)	

EAIR, exposure-adjusted incidence rates; AE, adverse events; PYE, Patient Years of Exposure

Safety- G-CSF use

Table S4. Growth Factor Use in Patients With Pretreated HR+/HER2- Metastatic Breast Cancer.

	SG (N = 268) n (%)	TPC (N = 249) n (%)
Total G-CSF use	144 (54)	83 (33)
As prophylaxis	94 (35)	53(21)
As treatment	75 (28)	47 (19)

G-CSF, granulocyte colony-stimulating factor; TPC, treatment of physician's choice

04

Discussion

Efficacy

- 34% reduction of disease progressed or death
- Significant benefit in landmark analysis (6 mon and 12 mon)
- For heavily treated patients
  (Prior 3 lines + all accepted CDK 4/6 inhibitor)
- For poor prognosis patients
  (Heavily treated, visceral metastases, ≥ 65 y/o)
- OS not significant yet

Comparison with previous trial

	Following time (mon)	PFS (mon)
Phase I/II IMMU-132-01 basket study	11.5	5.5 (3.6-7.6)
TROPiCS-02	11.3	5.5 (4.2-7.0)
	Following time (mon)	PFS (mon)
EMBRACE	-	eribulin: median 3.7 (3.3-3.9) TPC: median 2.2 (2.1-3.4)
Study 301 (HR+/HER2-)	-	eribulin: median 4.2 capecitabine: median 4.6
Pooled EMBRACE and Study 301	-	eribulin: median 4.1 other chemotherapy: median 3.4
Eribulin v.s. vinorelbine RCT	-	eribulin: median 3.7 (3.3-4.1) vinorelbine: median 3.1 (2.8-3.4)
TROPiCS-02	9.8	TPC: median 4.0 (3.1-4.4)

Comparison with Destiny-Breast04

	TROPiCS-02	Destiny-Breast04
HR/HER2 status	543 HR+/**HER2-**	494 HR+/**HER2-low** 58 HR-/**HER2-low**
intervention	**Sacituzumab-govitecan** 10mg/kg Q3W on D1 and D8	**Trastuzumab-deruxtecan** 5.4mg/kg Q3W
control	TPC: eribulin, capecitabine, gemcitabine, or vinorelbine	TPC: capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel
Median prior lines of therapy	3 (0-8) lines of chemotherapy	3 (1-9) lines of therapy
Adverse event all grade > 30%	Neutropenia, anemia, diarrhea, nausea, alopecia, fatigue	Neutropenia, anemia, nausea, vomiting, alopecia, fatigue
PFS	5.5 mon vs. 4.0 mon HR = 0.66 (0.53-0.83)	HR+ cohort 10.1 mon vs. 5.4 mon HR = 0.51 (0.40-0.64)

Con… s… r…

HR/HER2 status	545 HR+/**HER2**-	558 HR-/**HER2- ow**
interv	…ovitecan on D1 and D8	**Tras… …uxtecar** 5.4m…
control	…, capecitabine, gemcitabine, or vinorelbine	TPC: …, eribulin, gemcitabine, paclitaxel, or nab-
Media… chem…		
Adverse event all grade	Neutropenia, anemia, diarrhea, nausea, …	Neutropenia, anemia, nausea, …
PFS	HR = 0.66 (0.53-0.83)	HR = 0.51 (0.40-0.64)

HER2 Immuno-histochemistry (IHC) → **0** | **1+** | **2+** | **3+**

HER2 In situ hybridization (ISH) → **–** | **+**

Classification → **HER2-negative** | **HER2-positive**

Treatment option → **HER2-0** | **HER2-low** | **HER2-positive**

Comparison with Destiny-Breast04

	TROPiCS-02	Destiny-Breast04
HR/HER2 status	543 HR+/**HER2-**	494 HR+/**HER2-low** 58 HR-/**HER2-low**
intervention	**Sacituzumab-govitecan** 10mg/kg Q3W on D1 and D8	**Trastuzumab-deruxtecan** 5.4mg/kg Q3W
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Adverse event all grade > 30%	Neutropenia, anemia, diarrhea, nausea, alopecia, fatigue	Neutropenia, anemia, nausea, vomiting, alopecia, fatigue
PFS	5.5 mon vs. 4.0 mon HR = 0.66 (0.53-0.83)	HR+ cohort 10.1 mon vs. 5.4 mon HR = 0.51 (0.40-0.64)

Limitation

Chemotherapy group 8% not treated

Visceral disease (95%) related to shorter PFS and higher neutropenia risk

Physician’s choice and prior chemotherapy with high heterogeneity

Hormone receptor status not accurate

Not real-time BICR assessment increasing censoring

After the study – 2nd interim analysis

Table: LBA76

	SG (n = 272)	TPC (n = 271)
Median OS, mo	14.4	11.2
HR (95% CI)	0.79 (0.65-0.96), *P*=0.02	
ORR, n (%)	57 (21)	38 (14)
Odds ratio (95% CI)	1.63 (1.03-2.56), *P*=0.035	
Median DOR, mo (95% CI)	8.1 (6.7-9.1)	5.6 (3.8-7.9)
TTD of Global Health Score / Quality of Life,[a] mo	4.3	3.0
HR (95% CI)	0.75 (0.61-0.92), *P*=0.006	
TTD of Fatigue,[a] mo	2.2	1.4
HR (95% CI)	0.73 (0.60-0.89), *P*=0.002	
TTD of Pain,[a] mo	3.8	3.5
HR (95% CI)	0.92 (0.75-1.13), *P*=0.42	

[a]Assessed by EORTC QLQ-C30D

OR, duration of response; TTD, time-to-deterioration.

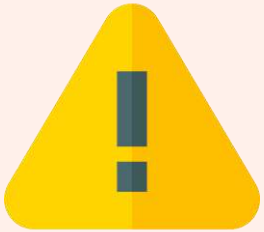
05

Conclusion and Clinical Benefit

Conclusion

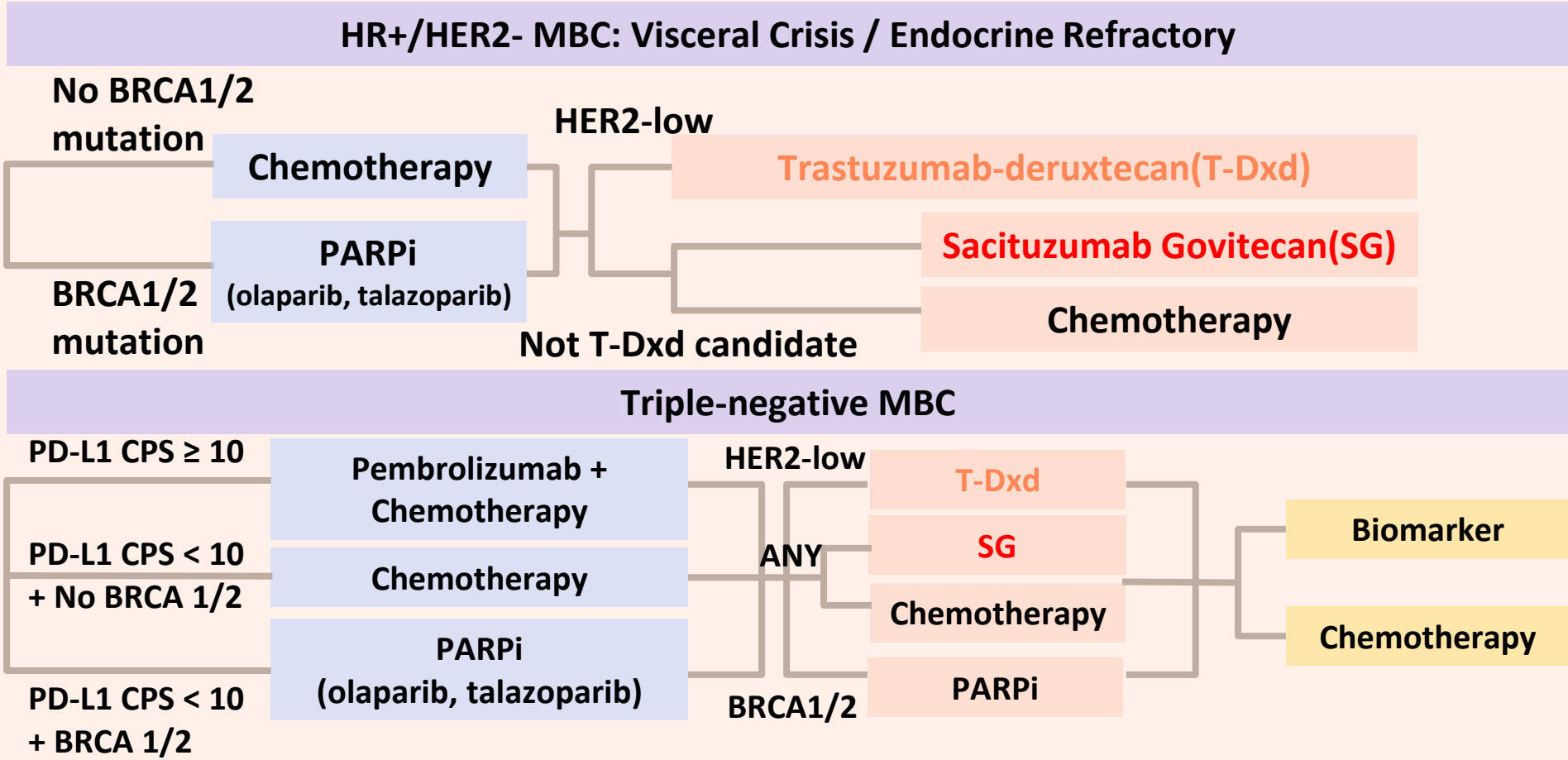
- New back lines ADC
- Seems to be better than chemotherapy
- Benefit in patients with visceral disease

- More adverse events (especially in nausea, diarrhea, alopecia)
- Current evidence only support in back line



- Monitor adverse event
- Carefully use in suitable patients

Clinical benefit



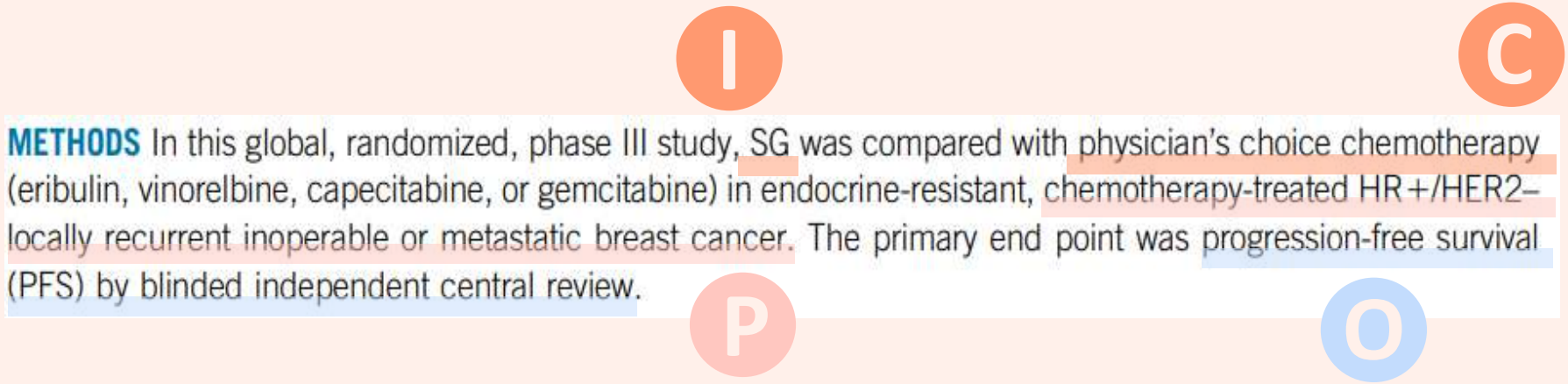
06

Appraisal

CRITICAL APPRAISAL SKILLS PROGRAMME

CASP

1. Did the study address a clearly focused research question?



Yes Can't tell No

2. Was the assignment of participants to interventions randomised?

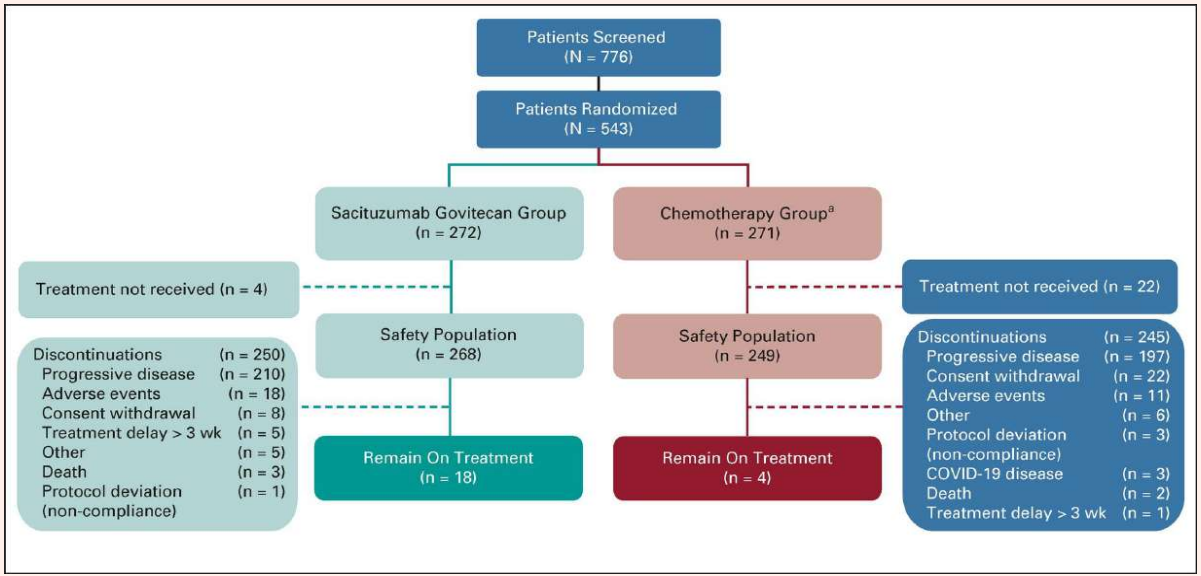
5.2 Subject Registration

At such time as a subject has been deemed eligible for the study and all required screening evaluations have been completed, the subject can be randomized. This will be done via an IWRS.

Randomization must occur on or before C1D1, such that dosing commences within 5 days after randomization.

Yes Can't tell No

3. Were all participants who entered the study accounted for at its conclusion?



-**ITT** Analysis Set
-All discontinued treatment participants were **given reasons**
-**Interim analysis** be performed when 272 or 350 OS events.

Yes Can't tell No

4. Blinding ?

Were the participants ‘blind’ to intervention they were given?

Yes Can’t tell No

Were the investigators ‘blind’ to the intervention they were giving to participants?

Yes Can’t tell No

Were the people assessing/analysing outcome/s ‘blinded’?

Yes Can’t tell No

Here, we provide the primary results of TROPiCS-02, a global, randomized, open-label, multicenter phase III study of SG versus single-agent chemotherapy in patients with locally recurrent inoperable or metastatic HR+/HER2– breast cancer (Data Supplement, online only).

End Points

The primary end point was PFS as determined by blinded independent central review (BICR) per the RECIST v1.1.[22] Secondary end points included OS, objective response, clinical benefit rate, duration of response, patient-reported outcomes, and safety (Data Supplement).

5. Were the study groups similar at the start of the randomised controlled trial?

TABLE 1. Baseline Characteristics and Treatment History of Patients

Characteristic	SG (n = 272)	Chemotherapy (n = 271)	All (N = 543)
Female, No. (%)	270 (99)	268 (99)	538 (99)
Median age, years (range)	57 (29-85)	55 (27-78)	56 (27-86)
Race or ethnic group, No. (%)			
White	184 (68)	178 (66)	362 (67)
Black	8 (3)	13 (5)	21 (4)
Asian	11 (4)	5 (2)	16 (3)
Others[b]	0	5 (2)	5 (1)
Not specified[b]	69 (25)	70 (26)	139 (26)
Visceral metastases at baseline, No. (%)	259 (95)	258 (95)	517 (95)
Liver metastases,[c] No. (%)	229 (84)	237 (87)	466 (86)
De novo MBC, No. (%)	78 (29)	60 (22)	138 (25)
Prior CDK4/6i use, months, No. (%)			
≤ 12	161 (59)	166 (61)	327 (60)
> 12	106 (39)	102 (38)	208 (38)
Unknown	5 (2)	3 (1)	8 (1)
Median prior chemotherapy regimens in the metastatic setting, No. (%)[d]	3 (0-8)[e]	3 (1-5)[e]	3 (0-8)[e]
0	1 (< 1)	0	1 (< 1)
1	8 (3)	2 (1)	10 (2)
2	104 (38)	118 (43)	222 (41)
≥ 3	159 (58)	151 (56)	310 (57)

TABLE 1. Baseline Characteristics and Treatment History of Patients

Characteristic	SG (n = 272)	Chemotherapy (n = 271)	All (N = 543)
Median prior chemotherapy regimens, No. (range)	4 (1-9)	4 (2-7)	4 (1-9)
Median prior anticancer regimens,[a] No. (range)	7 (3-17)	7 (3-16)	7 (3-17)
Most common prior anticancer therapy,[a] No. (%)			
Palbociclib	238 (88)	228 (84)	466 (86)
Capecitabine	226 (83)	234 (86)	460 (85)
Fulvestrant	235 (86)	223 (82)	458 (84)
Cyclophosphamide	204 (75)	209 (77)	413 (76)
Paclitaxel	210 (77)	196 (72)	406 (75)
Letrozole	185 (68)	210 (77)	395 (73)
Tamoxifen	160 (59)	165 (61)	325 (60)
Doxorubicin[a]	149 (55)	134 (49)	283 (52)
Exemestane	142 (52)	134 (49)	276 (51)
Most common prior anticancer therapy class in the metastatic setting,[c] No. (%)			
Endocrine therapy	268 (99)	269 (99)	537 (99)
CDK4/6i	267 (98)	270 (> 99)	537 (99)
Targeted agent	181 (67)	172 (63)	353 (65)
Immunotherapy	21 (8)	15 (6)	36 (7)
Chemotherapy	271 (> 99)	271(100)	542 (> 99)
Most common prior chemotherapy agent in the metastatic setting,[c] No. (%)			
Capecitabine	221 (81)	232 (86)	453 (83)
Paclitaxel	174 (64)	147 (54)	321 (59)
Eribulin[a]	95 (35)	88 (33)	183 (34)

Yes Can't tell No

6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?

- Schedule of procedure is clearly defined in protocol
- follow-up intervals are almost equal in two groups

Phase	Pre-treatment		Treatment					
Period	Screening	Baseline	Cycle 1		Cycle 2+ through last cycle		End of Treatment [a]	Follow-up
Day	-28 to -3	-3 to -1	Day 1	Day 8	Day 1	Day 8	Within +30 days of final treatment	Every 60 days
Assessments								
Informed consent	X							
Inclusion/exclusion criteria	X							
Demographics [b]	X							
Medical/surgical history [c]	X							
Prior anticancer therapy	X							
Prior radiation therapy	X							
Histology review to confirm HR+/Her2- (local)	X							
ECOG [d]	X		X		X		X	
Vital signs [e]	X		X	X	X	X	X	
Serum pregnancy test [f]	X	X						
Urine pregnancy test [f]					X		X	
Physical examination [g]	X	X	X	X	X	X	X	
ECG [h]	X		X					
Hematology [i]	X	X	X	X	X	X		
Chemistry [j]	X	X	X		X		X	
Urinalysis [k]	X	X			X			
Hepatitis B surface antigen, Hepatitis C antibody tests [l]	X							
UGT1A1 sample		X						
Biomarker samples [m]		X			X		X	
PK samples [i]			X	X	X	X	X	
Immunogenicity samples [i]			X		X		X	
Tissue sample[n]	X							
QOL assessments[o]		X			X [p]		X[q]	X[r]
Sacituzumab Govitecan administration[s,t]			X	X	X	X		
TPC administration[s]			As per standard of care					
CT or MRI tumor assessments[t]	X		Every 6 weeks for 52 weeks, then every 9 weeks					
CT or MRI of brain if known or suspected brain metastases	X		As clinically indicated or to confirm CR					
Bone scan or 18F-FDG PET scan[t]	X		Every 27 weeks or to confirm CR					
AEs/SAEs[u]	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	
Survival[v]								X
Progression/subsequent cancer treatment[w]								X

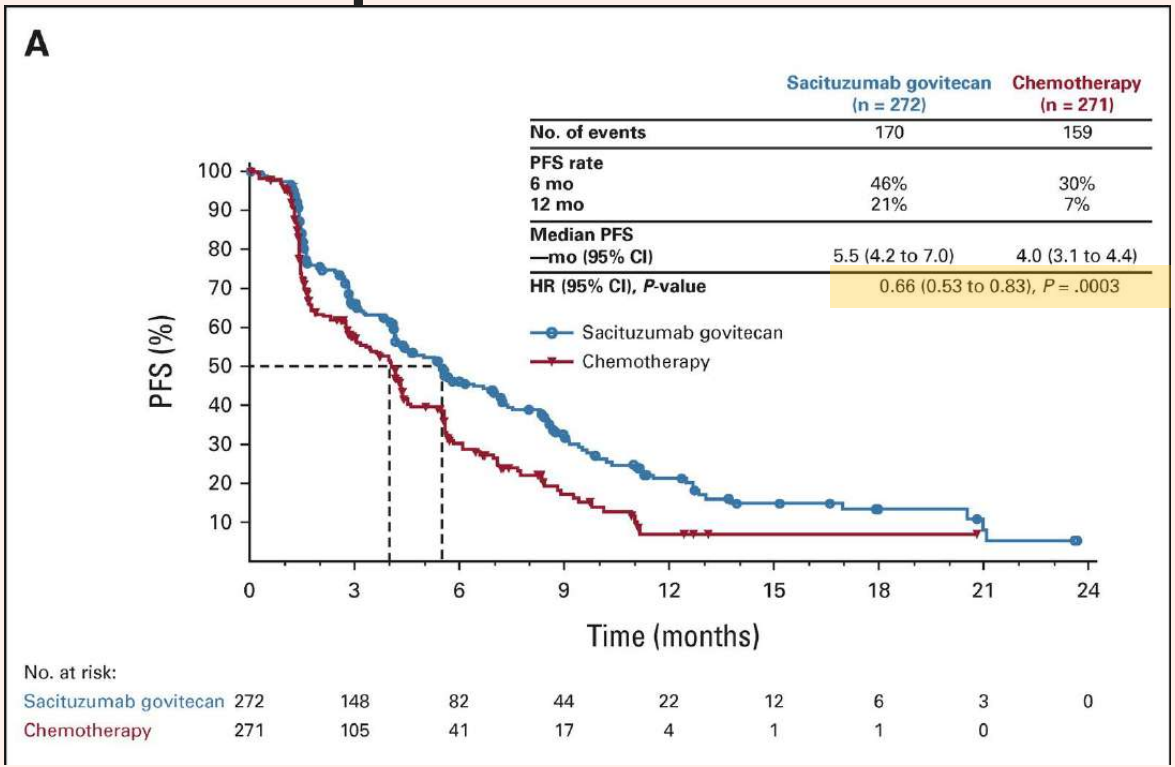
Yes Can't tell No

7. Were the effects of intervention reported comprehensively?

- **2-sided significance level of 0.0363. (No power calculation for interim analysis)**
- **p values** were reported
- The PFS and OS will be estimated by **Kaplan-Meier method** for each treatment group.
- **Outcomes were clearly specified** and assessed by blinded independent central review(BICR)
- **Hazard ratio (HR) and its 95% CI were estimated**, using stratified Cox proportional hazards regression model stratified by stratification factors.
- Drop-out rate is higher in chemotherapy group than Sacituzumab-govitecan.

Yes Can't tell No

8. Was the precision of the estimate of the intervention or treatment effect reported?



Yes Can't tell No

9. Do the benefits of the experimental intervention outweigh the harms and costs?

- PFS: 5.5 vs. 4.0 mon, HR=0.66, p=0.003
- OS: 13.9 vs. 12.3 mon, HR=0.84, p=0.14

- More adverse event: diarrhea, nausea, alopecia

- 74311 TWD/180mg, 594488 TWD/50kg/month

Yes Can't tell No

9. Do the benefits of the experimental intervention outweigh the harms and costs?

frontiers | Frontiers in Oncology

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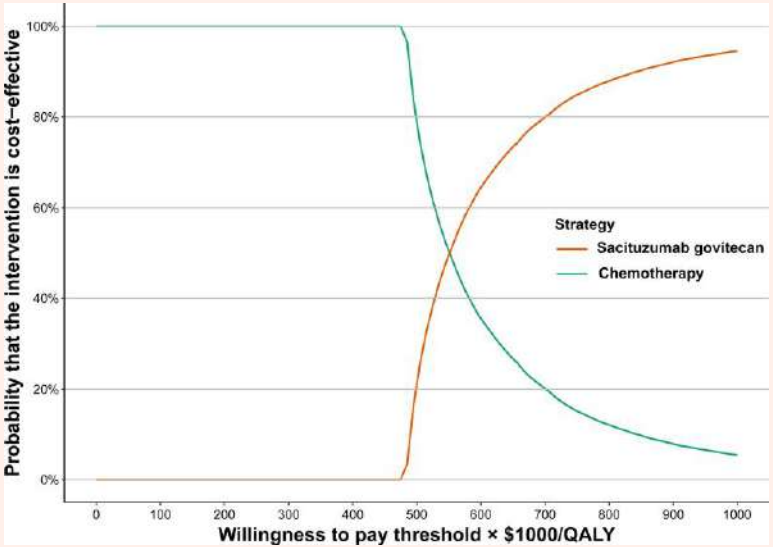
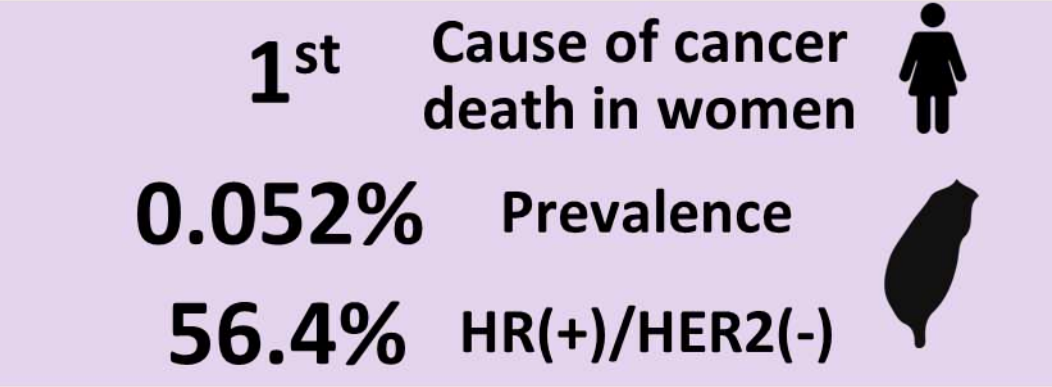
Cost-effectiveness of sacituzumab govitecan in hormone receptor-positive/ human epidermal growth factor receptor 2-negative metastatic breast cancer

Factor	Incremental change
ICERs, $	
Per life-year	467,013
Per QALY	612,772
INHB, QALY, at WTP threshold 150,000[a]	-0.668
INMB, $, at WTP threshold 150,000[a]	-100,208



Yes Can't tell No

10. Can the results be applied to your local population/in your context?



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White	184 (68)	178 (66)	362 (67)
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Asian	11 (4)	5 (2)	16 (3)
Others[a]	0	5 (2)	5 (1)
Not specified[b]	69 (25)	70 (26)	139 (26)

Yes Can't tell No

11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?

Sacituzumab-govitecan is a better 2nd-line therapy of MBC than chemotherapy if:

- Can afford the **price**
- Appropriate **manage adverse event**
- **Visceral disease**, **prior 2-4 chemotherapy** for MBC, **endocrine therapy** + **CDK 4/6 inhibitor** before

Yes Can't tell No

Thanks!

Do you have any questions?